case report
dystonia, causes
cimetidine, complications, dystonia

Exhibit J

Tagamet®-Induced Acute Dystonia

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A 30-year-old woman presented with an apparent acute dystonic reaction after only five doses of cimetidine (Tagamet®). The patient was on no other medications with the exception of oral contraceptives. Emergency administration of IV diphenhydramine HCl brought rapid reversal of this acute dystonic reaction without any neurological sequelae. To our knowledge, this is the first reported case of an acute dystonic reaction associated with cimetidine. [Romisher S, Felter R, Dougherty J: Tagamet®-induced acute dystonia. Ann Emerg Med October 1987;16:1162-1164.]

INTRODUCTION

Since cimetidine was introduced, there have been numerous reports of neurologic side effects associated with its use.[1-7]

We report a case of cimetidine-associated acute dystonia in a patient after only 30 hours of therapy.

CASE REPORT

A 30-year-old woman was seen because of severe right-sided mandibular pain, ipsilateral trismus, and dysphonia.

The patient had been placed on ranitidine (Zantac®) 150 mg twice daily one week earlier because of suspected peptic ulcer disease. After four days of therapy, her physician discontinued the medication because she complained of intolerable gastrointestinal upset. Two days later, cimetidine (Tagamet®) 300 mg qid was started. The patient took the fifth dose 12 hours prior to admission. Approximately nine hours prior to admission, she noticed the sudden onset of right-sided mandibular pain. Several hours prior to admission, she developed right-sided trismus with associated dysphonia. When walking, there was involuntary turning in of her right foot.

300 mg 4x/day
(1200 mg/day)

The medical history was significant only for a patent foramen ovale that was corrected surgically in childhood. Medications included oral contraceptives for more than one year and cimetidine. The patient denied the use of any other prescription or nonprescription medication or the use of illicit drugs. In addition, she denied mandibular trauma, fever, chills, or symptoms of odontal or pharyngeal pathology.

On physical examination, the patient's vital signs were as follows: pulse, 88; respirations, 18; blood pressure, 118/88 mm Hg; and temperature, 37.3 C. She was alert and oriented with impairment in phonation. There was marked spasm and pain of the right-sided masticatory muscles with deviation of the mandible to the right. The uvula was also deviated to the right, and there were tongue fasciculations. No lingual movements or dysphagia were noted. Pupils were equal and reactive and extraocular muscles were normal without any evidence of oculogyric dysfunction. The neck was supple without torticollis or retrocollis. Cardiac examination revealed a regular rhythm with a split first heart sound. Right ankle stiffening with "pipe-stem" rigidity was present despite normal reflexes with absent clonus in all four extremities. Gait testing revealed difficulty in ambulation because of a stiffened right ankle. The remainder of the physical examination was normal.

A urine screen for phenothiazines was obtained. A peripheral IV line of 5% dextrose and ½ normal saline was placed and she was given 50 mg of diphenhydramine HCl IV with immediate relaxation of the right-sided mus-

cles of mastication. There was marked improvement in phonation. The uvula remained deviated to the right, but there were no longer any tongue fasciculations. The right ankle showed absent rigidity to range of motion. No neurological abnormalities were found and gait testing was normal.

The patient was observed in the emergency department for approximately 90 minutes and discharged home with instructions to discontinue cimetidine and continue oral diphenhydramine HCl 50 mg four times per day for 48 hours. We re-examined the patient at 24 and 48 hours after her initial presentation. Complete return of normal speech and fifth cranial nerve function were noted. The uvula was in the mid-position and was no longer deviated.

Urine ferric chloride assay for phenothiazines done on admission was negative.

DISCUSSION

Acute dystonia is an extrapyramidal side effect (EPS) of antipsychotic medications and related compounds characterized by sudden, involuntary, intermittent tonus of a muscle or group of muscles.[8,10]

Any voluntary muscle group may be involved, but those of the head and neck are most frequently involved in adults.

Acute dystonias and dyskinesias are the least frequent but most dramatic forms of EPS.[8] However, dystonic reactions are now reported with increasing frequency when associated with neuroleptic use; rates may approach 50%.[11] Symptoms arise suddenly and may be frightening to the patient and observers.

Drugs that alter the dopamine-mediated function of the basal ganglia have been implicated in producing EPS. The drugs most notably responsible include neuroleptic agents used to treat psychosis, antiemetics such as trimethobenzamide and prochlorperazine, and the antireflux agent metaclopramide.[1,8,10,12] However, such other drugs as tricyclic antidepressants,[10] heroin,[13] benzodiazapines,[10] L-Dopa,[14] and ketamine[14] have been reported.[10]

The possibility of an acute dystonic reaction increases with increasing dosage and frequency but can occur after a single dose. Goldfrank and co-workers[15] believe the reactions are "idiosyncratic" ... This

reaction usually occurs within 24 to 72 hours of the first dose or after an increase in the maintenance dose.[9]

Cimetidine is a histamine receptor antagonist that is the structural analogue of histamine used in the treatment of peptic ulcer disease. The drug has no known effect on central dopaminergic pathways. CNS reactions have been reported with cimetidine therapy and are reversible on discontinuing the medication.[2] Predisposing factors to the development of this side effect include older age,[2,3] renal and hepatic impairment,[2,4] high-dose medication,[2,5] pre-existing psychiatric illness,[2,6] and simultaneous treatment with psychotropic medication.[2,6]

Only one previous case of extrapyramidal symptoms has been reported, and was associated with cerebellar syndrome.[7] These symptoms occurred in a 74-year-old man following a 1 g per day dose for 18 days. Renal and hepatic impairment were absent. However, the patient had preexisting cerebral vascular disease and dementia, and it was difficult to determine if cimetidine was the cause of the reaction. The patient had had previous acute confusional states.

Our patient was in excellent health with no predisposing factors in the development of acute dystonia or trismus. She had no history of neurologic or psychiatric illnesses. Infectious etiologies were not apparent. Toxicological screen was not obtained on other etiological agents that might cause an acute dystonic reaction because of the reliability of the patient's history. She was on no other medications that would confound the possibility of an acute dystonic reaction due solely to cimetidine. Finally, there was an adequate "wash out" period between the time she discontinued ranitidine and began cimetidine.

Emergency treatment of acute dystonia entails discontinuing the suspected offending agent and anticholinergic medication to offset cholinergic dominance. Parenteral diphenhydramine HCl or benztropine mesylate are the most familiar agents. However, other medications such as biperiden or trihexyphenidyl can be used.[9]

The emergency administration of diphenhydramine HCl 50 mg IM or slow IV push is one of the treatments of choice in adults.[9,10] Benztropine mesylate may be given as an alter...

Lee[16] to be the treatment of choice because of quicker recovery time and less drowsiness when compared to diphenhydramine HCl. Benztropine mesylate may be given at 2 mg IM or IV; however, the exact dose in children has not been fully documented.[9,10]

Despite the relatively rapid and dramatic recovery with these agents, there may be recurrences. To prevent them, Corre[10] recommends sending the patient home on oral diphenhydramine 50 mg three to four times daily for up to 72 hours.

SUMMARY

We present a case of an acute extrapyramidal side effects associated with cimetidine. The presenting symptomatology was typical of EPS, and other potential causes of EPS such as drugs or underlying medical problems were not present. While certainly not occurring frequently in patients treated with cimetidine, it should be considered in the differential diagnosis of any patient presenting with an acute dystonic reaction.

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